Patent No. 4,843,837). Moreover, claims 2, 3 and 6-8 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wisniewski and Wu article and further in view of Baldus et al. (U.S. Patent No. 4,178,776).

Claim 18 of the present application recites a method for thawing a frozen biopharmaceutical solution. The method includes heating the biopharmaceutical solution when at least a portion of the biopharmaceutical solution is frozen by using a heating element coupled to a container which contains the biopharmaceutical solution. The method further includes inducing oscillatory motion to the biopharmaceutical material to thaw the at least a portion of the biopharmaceutical solution using an oscillatory driver adapted to be coupled to the biopharmaceutical solution. The oscillatory motion has a frequency in a range from about 0.01Hz to less than about 20 Hz.

The Wisniewski and Wu article teaches a mechanical shaker platform being used to provide agitation during thawing. However, there is no indication of oscillatory motion, i.e., back and forth motion, being induced to a biopharmaceutical solution to thaw at least a portion of the biopharmaceutical solution, as is recited in claim 18. Oscillation is defined on the Merriam-Webster online dictionary (see www.M-W.com) as "to swing back and forward like a pendulum", while agitate is defined as "to move with an irregular, rapid, or violent action." Instead of providing oscillatory motion, the device in the Wisniewski and Wu reference merely recites a shaker platform. Thus, the platform in this reference merely shakes or vibrates without oscillation.

Moreover, agitation and oscillatory motion are described on pages 13 and 14 of the specification as being different concepts. Oscillation refers to back and forth movement which is described on page 13 as occurring via various oscillation drivers. Agitation may be further added to oscillatory movement as described on page 14. Thus, agitation and oscillation are not equivalent if agitation can be provided in addition to oscillatory movement. Since the Wisniewski and Wu reference refer to agitation being provided by the mechanical shaker platform and oscillatory motion is induced in the present invention as recited in claim 18, the features of claim

18 are not taught nor suggested by the cited reference. Therefore, it is respectfully submitted that claim 18 is not anticipated by the Wisniewski and Wu reference. Further, the dependent claims are believed not to be anticipated for these reasons and for their own additional features.

Regarding the alternative obviousness rejections, the Wisniewski and Wu article does not teach nor suggest oscillation but refers instead to agitation provided on a mechanical shaker platform. Such a stationary platform does not move from its resting place, and therefore it cannot oscillate, e.g., move back and forth. There is no suggestion nor motivation taught of the desirability of moving a tank containing biopharmaceutical material back and forth, as recited in claim 18. Also, the Office Action refers to the shaker platform being capable of harmonic and disharmonic motion. However, such motion is also not taught nor suggested by the cited reference. Instead, the reference refers to agitation which is different from oscillation whether harmonic or disharmonic.

Moreover, in accordance with the present invention, oscillation may be preferred over agitation in the thawing of biopharmaceutical materials due to the sensitive nature of such materials. Specifically, low frequency motion may protect biopharmaceutical materials such that there is an absence of mechanical or hydrodynamic sheer in a softened glassy state between the ice crystals, as described on pages 8 and 9 of the present appliction. Such low frequencies can gently rearrange the ice crystals to cause release and melting of such crystal and dissolution of the glassy state. Thus, a low frequency motion, as is recited in claim 18, is preferred to protect biopharmaceutical materials from being damaged during thawing. Therefore, the oscillatory motion at low frequency, which is recited in claim 18 of the present application, is preferred over an agitational motion at a higher frequency disclosed, for example, in the Wisniewski and Wu reference due to the sensitive nature of the biopharmaceutical materials. Moreover, there is no suggestion nor motivation in the cited reference to provide such a low frequency motion. Therefore, it is respectfully submitted that claim 18 is not made obvious by the Wisniewski and Wu reference. The dependent claims are believed not to be obvious for these reasons and for their own additional features

The obviousness rejections of the dependent claims over Baldus et al. and Peppers are also believed to be overcome due to their reliance on the § 102 application of the Wisniewski and Wu reference to base independent claim 18. Therefore, these claims are believed to be allowable for the same reasons as independent claim 18 and for their own additional features.

Further, prior art references may be combined in an obviousness rejection only if such a combination of the particular references is proper. It is respectfully submitted that the Peppers and Baldus et al. references are non-analogous to the subject matter of the present application and therefore their combination is improper.

A determination of whether or not a reference is non-analogous is two-fold. First, it must be decided if the reference is within the field of the inventor's endeavor. If it is not, then it must be determined whether the reference is reasonably pertinent to the particular problem the inventor sought to solve. Heidelberger Druckmaschinen AG v. Hantscho Commercial Products Inc., 30 U.S.P.Q.2d 1377, 1379 (Fed. Cir. 1994); In re Wood, 599 F.2d 1032, 202 U.S.P.Q. 171, 174 (CCPA 1979).

As set forth in the technical field, the present invention is directed generally to the thawing of biopharmaceutical solutions and more particularly to enhanced thawing of biopharmaceutical solutions using oscillatory motion. In contrast, the Peppers reference is directed to methods and apparatus for making large quantities of block or cubed ice. The Baldus et al. reference is directed to a method and apparatus for thickening of solution containing crystallizable solvent and more particularly to an improved system for crystallizing a solvent component from the solution to form a concentrate or inspissat therefrom. Further, Baldus et al., is directed to the freezing of ice crystals from aqueous solutions in order to form concentrate thereof. It is evident that the technical fields of the cited references are not the same as that of the present invention, since they are not directed to biopharmaceutical materials and more specifically not to thawing biopharmaceutical materials using oscillatory motion.

As set forth in the Background Art section of the present application, the main problem sought to be solved is to develop a method for thawing biopharmaceutical materials while preserving the activity of the material, e.g., without damaging the material. In contrast, the Peppers reference sought to create an improved ice block maker which utilizes vibration to release ice blocks from the evaporator thereof. Further, the Baldus et al. reference sought to solve the problem of providing a method and apparatus for the freezing of solvent components from a solution. These problems are obviously quite different. Thus, Peppers nor Baldus et al. is reasonably pertinent to the particular problem of thawing biopharmaceutical material. Since the cited references are not directed to applicant's field of endeavor, nor reasonably pertinent to the problem sought to be solved, Applicant submits that Pepper and Baldus et al., are non-analogous art, and, therefore, improperly applied. Thus, the non-analogous nature of these references is a further reason that the dependent claims are not obvious and are believed to be allowable.

Also, as requested by the Examiner, a copy of the Quan article, entitled "Effects of Vibration on Ice Contact Melting Within Rectangular Enclosures" is included herewith. Further, the Examiner has requested English translations of German language PCT Publication No. WO 97/24152 and German reference No. DE 3047784A1. Regarding the former reference, U.S. Patent No. 5,999,701 to Schmidt is provided herewith, which is the U.S. National Phase patent for the PCT application. Also, U.S. Patent No. 4,473,739, which was previously provided is believed to be similar to German language reference DE 3047784 as is evident by the identical figures and common assignee. Thus, it appears that the corresponding U.S. patents already of record are sufficient for examination of their counterpart German language references, particularly where translations are not available. See Ex. Parte Jones, 62 USPQ 2d 1206 (BD. Pat. App. & Inter. 2001).

Schmidt discloses an electrical quick-thawing apparatus for quickly thawing frozen liquids contained in syringes, infusion bottles, or infusion solution bags. The device includes an electrical oscillating driver in the form of a base speaker. The frozen liquid is inserted in a longitudinal cavity of the device and driven vertically by the speaker. The speaker is capable of providing a vibrating effect having a frequency in a range of 20 Hz to 300 Hz. However, there is no

indication of the speaker moving in a frequency of less than 20 Hz, nor moving in a frequency between 0.1 Hz and 20 Hz, as is recited in claim 18 of the present application. In fact, column 3 of the specification of Schmidt states that the preferred frequency range is between 50 Hz and 100 Hz, which is substantially different than the range recited in claim 18 of the present application. Further, the preferred range indicated in column 3 teaches away from the range recited in claim 18 of the present application, since an increase of the lower limit of the frequency range from 20 Hz is taught to be desirable as opposed decreasing such a lower limit. Thus, one skilled in the art reading U.S. Patent No. 5,999,701 would be taught that a higher frequency range is desirable as opposed to a lower one. Therefore, one skilled in the art would not be motivated to utilize frequencies lower than those described in Schmidt, such as those recited in claim 18 of the present application.

Further, the Schmidt device does not disclose a heating element coupled to a container which contains biopharmaceutical solution. In Schmidt, the liquid is thawed by vibration not by the combination of oscillatory movement and heating via a heating element. Moreover, given the small size of the vials, e.g., 50 ml, thawed in Schmidt, there would be no reason or suggestion to utilize a heating element in such an apparatus. First, since small vials are thawed the motivation to decrease thaw time is obviated. Second, the references do not provide any basis for using a heating element for such small volumes. Thus, there is no suggestion or motivation in Schmidt (or any of the other references), when considering the reference as a whole, to provide for a container coupled to a heating element which is subject to oscillatory motion, as is recited in claim 18 of the present application.

Thus, Schmidt does not teach nor suggest the features of claim 18 of the present application. Therefore claim 18 is believed to be in condition for allowance and the dependent claims are believed to allowable for these reasons and for their own additional features.

CONCLUSION

It is believed that the application is in condition for allowance, and allowance of all claims is respectfully requested.

Attached hereto is a marked up version of the changes made to claim 1. The attached page is captioned "**Version with markings to show changes made**."

If a telephone conference would be of assistance in advancing prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him/her at the number provided.

Respectfully submitted,

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"**VERSION WITH MARKINGS TO SHOW CHANGES MADE**."

18. ***(Amended)*** A method for thawing a frozen biopharmaceutical solution, the method comprising:

heating the biopharmaceutical solution, when at least a portion of the biopharmaceutical solution is frozen, using a heating element coupled to a container which contains the biopharmaceutical solution; and

inducing oscillatory motion to the biopharmaceutical solution to thaw the at least a portion of the biopharmaceutical solution using an oscillatory driver adapted to be coupled to the biopharmaceutical solution[.]; and

wherein a frequency of the oscillatory motion of the oscillatory driver ranges from about 0.01 Hz to less than about 20 Hz.